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AKZO NOBEL INC.
INTELLECTUAL PROPERTY DEPARTMENT
7 LIVINGSTONE AVENUE
DOBBS FERRY, NY 10522-3408

EXAMINER	
ISSAC, ROY P	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/781,493	HAAN DE, PIETER	
	Examiner	Art Unit	
	Roy P. Issac	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a divisional of 09/723412 (November 28, 2000), now abandoned. The preliminary amendment filed on 7/9/2004 with the present application is acknowledged wherein, claims 1-12 are cancelled and new claims 13-17 are submitted. Claims 13-17 are now pending, and are examined on the merits.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions of tibolone having particle size 14.4-22.8 μm, does not reasonably provide enablement for compositions of any other particle sizes. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Particle size, essential to the practice of the invention, but not included in the claims renders the claims non-enabling. The disclosure states that, "The main requirements for the present invention include that a solid pharmaceutical composition of tibolone is provided, and that tibolone, when contained the dosage form, has a particle size as defined above." (Page 3, First Paragraph of Detailed Description of the Invention). The particle size is defined in the summary of the invention as below 22.8μm and preferably below 20 μm. (Page 2, First paragraph of the summary of the invention, lines 3-6). Examples in the specification include particle sizes in the range of 14.4-48.2 μm. Note that examples where particle size is above 22.8 μm achieves bioavailability levels less than the solution level. (Page 15, Table and Figure 2) Claims 13 and 16 do not contain any particle size limitations.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The Nature of the invention: The claimed invention is a therapeutic method for the treatment and prevention of menopausal complaints. Specifically, the invention is the use of tibolone in particle sizes below 22.8μm for the treatment of menopausal complaints.

The state of the prior art: The state of the prior art includes the use of tibolone for the treatment of menopause and recognizes the correlation between particle size and bioavailability. The special effect of one of the two metabolites of tibolone being more bioavailable due to particle size below 22.8μm is not known in the art.

The relative skill of those in the art: The relative skill of those in the art is high, with a typical practitioner having obtained a PhD or equivalent advanced degree.

The predictability or unpredictability of the art: There is a generally recognized correlation between particle size and bioavailability in drugs. However, the optimal particle size varies for different drugs and methods of making particles of specific sizes also vary with different drugs. The optimal particle size for each drug and the method of achieving specific sizes and bioavailability are unpredictable.

The Breadth of the claims:

Claims 13 and 16 does not limit drug particle size and as such, includes tibolone composition of any size.

The amount of direction or guidance presented:

The disclosure states that, "The main requirements for the present invention include that a solid pharmaceutical composition of tibolone is provided, and that

tibolone, when contained in the dosage form, has a particle size as defined above." (Page 3, First Paragraph of Detailed Description of the Invention). The particle size is defined in the summary of the invention as below 22.8μm and preferably below 20 μm. (Page 2, First paragraph of the summary of the invention, lines 3-6). Specification includes examples of particle sizes in 14.4-48.2 μm ranges. (Specification, Page 15, Table of Tibolone Drug Product Batches). However, there is no guidance to achieve the claimed effect of increased bioavailability at other particle sizes.

The presence or absence of working examples: The specification teaches particle sizes from 14.4μm to 48.2 μm. (Specification, Page 15, Table of Tibolone Drug Product Batches). Furthermore, the specification teaches that achieving a particle size of below 22.8μm is critical. (Discussion above). Working examples of particle size above 22.8μm does not achieve a bioavailability level above that of a solution. (Figure 2).

The quantity of experimentation necessary: In order to attain bioavailability at the level described in claims 13 and 16, particle size is a critical factor. The specification only teaches particle sizes in the range of 14.4μm to 48.2 μm. Of the specified range, a particle size of below 22.8μm is critical in achieving the desired bioavailability level. (Discussion above). Specification does not teach how to achieve bioavailability level above the solution standard for particle size above 22.8μm.

Particle size is an important factor in the dissolution rates of drugs. (Cooper, et. al., Page #1512, Column 2, Paragraph 3, lines 7-14, PTO-892, Cited by the examiner). The dissolution rate of a drug is a function of the intrinsic solubility of its particle size. A number of poorly soluble drugs have demonstrated that particle size reduction can lead

to an increased rate of dissolution and higher oral bioavailability. Majority of the studies have involved mechanical size reduction to particles larger than 1 μm. (Liversidge et. al., Page # 92, column 1, Paragraph 2, lines 1-17, PTO-892, Cited by the examiner). The instant application teaches that the particle size below 20 and 22.8 μm are critical to the present invention. However, claims 13 and 16 does not contain any limitations for particle size. Thus, claims 13 and 16 are not enabled beyond the ranges of 14.4-22.8μm.

Therefore, in view of the Wands factors, as discussed above, especially the breadth of the claims, the unpredictability of the art, and the lack of guidance or working examples in all ranges, Applicants fail to provide information sufficient to practice the claimed invention for the treatment of conditions claimed herein absent undue experimentation.

Claims 13-17 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of menopausal symptoms, does not reasonably provide enablement for prevention of menopausal symptoms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a

disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The Nature of the invention: The claimed invention is a therapeutic method for the treatment and prevention of menopausal complaints. Specifically, the invention is the use of tibolone in particle sizes below 22.8μm for the treatment of menopausal complaints.

The state of the prior art: The state of the prior art includes the use of tibolone for the treatment of menopausal symptoms. The teachings do not include the prevention of menopausal symptoms by the use of tibolone.

The relative skill of those in the art: The relative skill of those in the art is high, with a typical practitioner having obtained a PhD or equivalent advanced degree.

The predictability or unpredictability of the art: Prevention of menopausal symptoms is not the same as the treatment of said symptoms. In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method,

one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?

2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely suppress all symptoms?

3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active agent accumulate in the subject's tissues? Is the minimum dose necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

For this reason, many of the therapies that are useful for treating a disease are not useful preventing the disease. For example, antibiotics, chemotherapeutics and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer.

The Breadth of the claims: Claims cover both treatment and prevention of menopausal complaints by the administration of tibolone. "Prevention" is neither defined nor mentioned in the specification.

The amount of direction or guidance presented:

The specification cites the use of tibolone for the treatment (not prevention) of menopausal complaints. (Specification, Page 1, Second Paragraph).

There are at least 11 symptoms associated with menopause. (Alder, et. al., Page 19, Column 1, Second paragraph under Introduction, lines 1-4, PTO 892, Cited by the examiner). The specification does not indicate which of the many complaints of menopause would the novel method of use for tibolone, as claimed, will prevent or treat.

There is no guidance given for the prevention of menopausal complaints given within the specification. The specification states that particle size below 22.8μm favors one of the two metabolites of tibolone. (Specification, Page 2, first paragraph under "Summary of the invention," lines 1-3). Since there are many complaints associated with menopause, it is not clear which of the menopausal complaints will be improved by the increased bioavailability of one of the metabolites.

Again, there is no guidance as to which of the menopausal complaints will be "prevented" by the use of tibolone as claimed.

The presence or absence of working examples: There are no working examples of the treatment of menopausal complaints provided in the specification. There are no working examples for the prevention of menopausal complaints given in the specification. Furthermore, there are no specific "menopausal complaints" that are demonstrated to be effected by the claimed method of use.

The quantity of experimentation necessary:

Tibolone's usefulness as a drug to treat complaints associated with menopause is no guarantee that it will be effective in preventing menopausal complaints from occurring in the long term. Because no guidance is given for the use of the claimed

therapeutic method for the long-term prevention of disease, one skilled in the art wishing to practice the invention would be unable to do so without first gathering information as to the long-term effectiveness of the therapy.

In particular, one skilled in the art would need to know whether the regular administration of tibolone in the claimed form over the long term would adversely affect the health of the subject. Additionally, one skilled in the art, in order to practice the invention for prevention of disease would need to know whether the preventive effect remains potent over the long term. Unless the therapy absolutely eliminates all "menopausal complaints" over the long term, the drug cannot be considered a preventive therapy.

Furthermore, it is not clear which of the menopausal complaints will be prevented by the use of tibolone in its claimed form. Since the claimed use favors one metabolite, it is not expected to produce the same results in patients as other forms of tibolone.

In order to answer these questions, in the absence of any existing data, one skilled in the art, in order to practice the invention, would have to undertake long-term animal tests, preferably over a period of years, preferably involving a relatively long-lived experimental animal such as dogs or sheeps. Accomplishing such a task for the myriad of symptoms that can be considered menopausal complaints would require an undue amount of experimentation for the practice of full range of the claimed invention.

Genetech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent

protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, especially the breadth of the claims, the unpredictability of the art, and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for the prevention of diseases claimed herein absent undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13, the only independent claim in the present application, refers to a "level above," which is not clearly defined in the specification. The lack of upper limit renders the claim indefinite.

Claim 13 is further rejected under 35 U.S.C 112, second paragraph, for the following reason. One of ordinary skill in the art would not be able to clearly ascertain the scope of the recitation in claim 13, "wherein the pharmaceutical formulation has a bioavailability, in vivo, of a 3^{α}-OH tibolone at a level above that provided by a solution of tibolone, wherein the amount of tibolone in the immediate-release peroral dosage unit and in the tibolone solution are substantially the same." There are multiple methods

available for the oral intake of tibolone, including tablets, solution, and mixed with pharmaceutical carriers with varying effects on its bioavailability. Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to the method of treatment encompassed by the recited phrase herein.

Claim 14 is further rejected under 35 U.S.C 112, second paragraph, for the following reason. Claim 14 refers to a particle size "below about 22.8 μM". The specification does not define "below." The lack of lower limit in the claimed range renders the claim indefinite.

Claim 15 is further rejected under 35 U.S.C 112, second paragraph, for the following reason. Claim 15 refers to a particle size "below about 20 μM". The specification does not define "below." The lack of lower limit in the claimed range renders the claim indefinite.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Sas et. al. (U.S. Patent No. 5,037,817, PTO-1449, Included by the applicant).

Sas et. al. teaches the use of Tibolone for the treatment of menopausal complaints. (Claim 7, Column 6, lines 30-37). The '817 patent also teaches the use of 2.5mg dosage of tibolone. (Column 4, Example 6, lines 40-50). Tibolone is also known

as (7α-17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one. (Specification, Page 1, Paragraph 1).

Applicant's specification shows that the Tibolone in '817 patent can be the same product as the Tibolone product used in the claimed method for treatment of menopausal complaint. The applicant notes;

> "Incidentally, with the benefit of hindsight, one can asses that the product as produced in Example 1 of US 5,037,817 satisfies the same criteria. This, however, is to be regarded as truly accidental, since a teaching on the bioavailability of Org A, let alone of the influence of particle size thereupon, cannot be derived from US 5,037,817. (Specification, Page 2, Fourth Paragraph)."

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In *In re Crish*, 393 F.3d 1253, 1258, 73 USPQ2d 1364,1368 (Fed. Cir. 2004). *See* MPEP 2110.4.

In case of the present application, the property, increased bioavailability of one of the metabolites of the drug tibolone due to small particle size, is inherently present in

the composition of '817 patent. Furthermore, the use of tibolone for menopausal patients is expressly taught in the '817 patent.

The recitation in claim 16, "wherein a sample of said pharmaceutical formulation containing 2.5mg of tibolone is exposed to a 0.25% sodium lauryl sulfate solution and dissolution rate is measured, a $t_{50\%}$ value about 23.1 minutes is obtained" is not considered further limiting the claim. The phrase recites an inherent property of the claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lippuner, K (PTO-892, Cited by the applicant), in view of Bourke et. al (PTO-982, Cited by the examiner).

Lippuner et. al. teaches the use of tibolone for the treatment of menopausal complaints and teaches the use of 2.5mg dosage and the oral intake of tibolone. (Page 806, Abstract).

Lippuner does not expressly teach the use of particle sizes below 22.8 μm.

Bourke teaches a method for increased bioavailability of pharmaceutical substances in vivo, in particular steroidal drugs. (Page 2, lines 10-13). Note that, tibolone is a steroidal drug. Bourke further teaches steroidal drugs with particle size less than 10μm. (Page 4, lines 8-13). Bourke also teaches to use of administration of steroids in capsule form. (Page 7, lines 2-5). Bourke further teaches that it is desirable to enhance bioavailability. (Page 2, lines 2-3).

Bourke did not compare the bioavailability of the 10μm steroid form with a steroid solution. However, there is nothing in the specification to indicate that a 10μm formulation according to Bourke will not have the same bioavailability as the 22.8μm or less described in the present invention.

As discussed above, the recitation in claim 16, "wherein a sample of said pharmaceutical formulation containing 2.5mg of tibolone is exposed to a 0.25% sodium lauryl sulfate solution and dissolution rate is measure, a $t_{50\%}$ value about 23.1 minutes is obtained" is not considered further limiting the claim. The phrase recites an inherent property of the claimed method.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to treat menopausal complaints by administering to patient in need thereof an effective amount of a pharmaceutical formulation in the form of an immediate-release peroral dosage unit, comprising tibolone, wherein the pharmaceutical formulation has a bioavailability, in vivo, of 3^{α}-OH tibolone at a level above that provided by a solution of tibolone, wherein the amount of tibolone in the

immediate-release peroral dosage unit and in the tibolone solution are substantially the same.

One of ordinary skill in the art at the time the invention was made would have been motivated to use tibolone for the treatment of menopausal complaints by administering to patient in need thereof an effective amount of a pharmaceutical formulation in the form of an immediate-release peroral dosage unit, comprising tibolone, wherein the pharmaceutical formulation has a bioavailability, in vivo, of 3^{α}-OH tibolone at a level above that provided by a solution of tibolone, wherein the amount of tibolone in the immediate-release peroral dosage unit and in the tibolone solution are substantially the same, since tibolone was well known for its effectiveness against menopausal complaints and the use of 10μm or less particle-size steroidal drugs were known to have more bioavailability.

Therefore, one of ordinary skill in the art would have reasonably expected that using tibolone in 10μm or less particle size would have more bioavailability.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Roy P. Issac
Patent Examiner
Art Unit 1623
April 28, 2006

S. Anna Jiang, Ph.D.
Supervisory Patent Examiner
Art Unit 1623